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Predictors of the course of illness in outpatients with schizophrenia: A prospective three year study

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ABSTRACT

The course of schizophrenia includes a combination of periods of remission and relapse. Previous studies focused on simple dichotomous outcomes and did not take into account the complexity of the course. Using data from a large 3-year follow-up study of schizophrenia, we described the different courses of schizophrenia. Of the 5950 patients with complete 3-year data, 38.7% never achieved remission (prolonged course), 15.7% achieved remission but relapsed and 45.7% achieved and maintained remission (persistent remission). Females, patients with better social functioning at baseline (living independently, in paid employment, socially active or having a spouse or partner) and with a shorter duration of illness had a more favourable course. Patients prescribed risperidone, quetiapine or depot typicals at the baseline visit were more likely to have a prolonged course than patients who started olanzapine. The results show that description of the long-term outcome of schizophrenia cannot be summarized with just one outcome variable.

1. Introduction

Schizophrenia is a heterogeneous disorder. Classical studies conducted in the 1970s and 1980s showed that the course of schizophrenia varies greatly among patients (Harding, 1988). Some patients show one or a few relapses over their lifetime, others present remission and relapse periods and some have a chronic course with persistent symptoms, with or without exacerbations. However, these early studies were mostly descriptive and rarely analyzed the factors associated with the different outcomes.

Studies that have analyzed predictors of the course of schizophrenia have used dichotomous outcomes: e.g., achieving remission or not achieving remission (Eaton et al., 1998), suffering or not suffering a relapse (Buchkremer et al., 1991) or experiencing or not experiencing a hospitalization (Eaton et al., 1992). These studies have shown that males tend to have a worse prognosis than females (Riecher-Rossler and Hafner, 2000), that patients with a younger age of onset tend to have a less favourable course (Lenior et al., 2005), that substance abuse increases the risk of relapse (Farris et al., 2003), that good social functioning is a powerful protective factor (Haro et al., 2006b) or that some medications seem to be associated with a more favourable course (Ascher-Svanum et al., 2004; Gianfrancesco et al., 2006b). However, these studies have not been able to describe the complexities of the course of schizophrenia, which is characterized by periods of better and worse clinical status and functioning.

The aim of the present report was to use data from the SOHO (Schizophrenia Health Outcomes) study, a 3-year follow-up study of the outpatient treatment of schizophrenia, to describe the different courses of schizophrenia in outpatients, defined by combining periods of better and poorer outcome. We also analyzed which socio-demographics and baseline clinical characteristics (symptom severity, social functioning) were associated with the different courses. A specific objective was to assess which antipsychotic medications were related to a better course.

2. Patients and methods

The SOHO study is a 3-year prospective observational study conducted in 10 European countries (Haro et al., 2003a). One thousand and ninety-six psychiatrists participated and enrolled at least one patient. Psychiatrists were mostly working in public (46.9%) or combined public and private (37.2%) practices.

The study was approved in all countries either at the site, regional, or national level, depending on the country and local regulations. Patient consent followed country regulations. All patients gave at least oral informed consent and written informed consent was obtained in Denmark, Italy, Portugal, Spain, Ireland, and the UK.

Participating psychiatrists offered enrolment to patients who met the following entry criteria: initiating or changing antipsychotic medication for the treatment of schizophrenia; presenting within the

Abbreviations: CGI, the Clinical Global Impression scale; CGI-SCH, Clinical Global Impression-Schizophrenia scale; SOHO, Schizophrenia Health Outcomes study.

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normal course of care in the outpatient setting or in the hospital when admission was planned for the initiation or change of antipsychotic medication and discharge planned within 2 weeks; at least 18 years of age; and not participating in an interventional study.

Since the initial objective of the SOHO study was to compare the outcomes of patients treated with olanzapine with those receiving other antipsychotics, the study was designed to provide two patient cohorts of approximately equal size: patients who initiated therapy with or changed to olanzapine; and patients who initiated therapy with or changed to a non-olanzapine antipsychotic. To achieve approximately equal numbers in the olanzapine and non-olanzapine groups, different sample fractions entered each cohort. This resulted in a stratified sample, with the olanzapine group as the 'over-sampled' stratum.

Effort was made to avoid interference with clinical practice. Investigators were instructed to make treatment decisions independent of the study and then evaluate whether patients were eligible for inclusion based on the entry criteria. The recruitment period was intentionally long and no minimum number of cases was required by each investigator. All patient health care was at the discretion of the participating psychiatrist. No instructions about patient care were included in the study description. Patients were followed up regardless of medication changes.

Data collection for the study occurred during visits within the normal course of health care. The routine outpatient visit at which patients were enrolled served as the time for baseline data collection. Subsequent data collection was targeted for 3, 6, 12, 18, 24, 30 and 36 months. For each data collection target, investigators were allowed to collect data up to one month before or after the target month. Patients who were not seen during the normal course of care within one assessment interval were not excluded from subsequent data collection.

Clinical severity was assessed using a scale based on the Clinical Global Impression (CGI), which evaluated positive, negative, cognitive, depressive and overall symptoms on the day of assessment. This was subsequently expanded and validated as the Clinical Global Impression-Schizophrenia scale (CGI-SCH) (Haro et al., 2003b), which evaluates symptom severity in the week before the day of assessment. The CGI and CGI-SCH are physician-rated scales with values ranging from 1 (not ill) to 7 (among the most severely ill patients). Verbal or physical hostility manifested by the patient was assessed by the participating psychiatrists in a single question (Has the patient exhibited verbal or physical hostility/aggression in the past 6 months?).

The number (%) of patients assessed at each of the following time points was: baseline, 10,218 (100%); 6 months, 9273 (90.8%); 12 months, 8848 (86.6%); 18 months, 8386 (82.1%); 24 months, 7913 (77.4%); 30 months, 7432 (72.7%); and 36 months, 7112 (69.6%).

3. Statistical analysis

Remission was defined as a score of 3 (mild severity) or less on the CGI overall severity score, the CGI positive symptoms score, the CGI negative symptoms score and the CGI cognitive symptoms score that was maintained for a period of six months or more (Haro et al., 2007a). In addition, the patient should not have been hospitalized during the period. Relapse was defined, for those patients achieving remission, as an increase in the score of the above CGI scales or being hospitalized (Haro et al., 2006a).

Three course patterns were defined:

1) Patients who achieved remission and maintained remission (Persistent remission).
2) Patients who achieved remission and had a relapse (Remission and relapse).
3) Patients who never achieved remission (Prolonged course).

Two multinomial regression models were used to analyze the baseline factors associated with the three courses of schizophrenia: one model used "chronic course" as the reference category and the other model used "persistent remission" as the reference category.

Many patients changed medication during the 3-year follow-up period (Haro et al., 2007b). Two analytical strategies taking into account medication changes were used to assess the impact of antipsychotic medication on the course of schizophrenia. In the first analysis, each patient was assigned to a medication cohort based on the medication they were prescribed at the baseline visit. In the second (sensitivity) analysis, the assigned medication was the medication the patient was taking at the beginning of the first remission period. For patients who did not achieve remission, the medication was that taken at the baseline visit.

Analyses were conducted on the 6770 patients with medication data available at all visits or at most one missing visit over the 3-year follow-up period. For patients with only one missing value for the three main analysis variables (CGI scores, hospitalization and medication), the missing values were imputed from the previous assessment. However, after imputation, 820 patients still had some missing values for the CGI or hospitalization which made it impossible to evaluate remission status in some of the 6-month periods. Thus, the final number of patients included in the present analyses is 5950 (58.2% of the patients included in SOHO).

4. Results

Of the 5950 patients analyzed, 2301 (38.7%) never achieved remission during the 3-year follow-up (prolonged course), 933 (15.7%) achieved remission but relapsed (remission and relapse) and 2716 (45.7%) achieved and maintained remission (persistent remission). Table 1 presents the socio-demographic and baseline clinical characteristics of the total patient sample and in the three subgroups by course type. As we can see in the last column of Table 1, the majority of patients (58%) were male and mean age was 40.3 years. Mean duration of illness was 11.9 years and 9% of patients had never been treated for schizophrenia before inclusion in the study.

Table 1 also shows the differences at baseline between the three groups of course types. The proportion of males in the prolonged course group was higher than in the persistent remission group.

Table 1
Baseline clinical and socio-demographic characteristics by course type

	Persistent remission	Remission and relapse	Prolonged course	Total
	Percentage			
Male	55	58	62	58
Never treated before baseline	12	10	6	9
Living independently	51	51	41	47
Paid employed	26	22	11	19
Socially active	74	70	60	68
Spouse	33	32	24	29
Concomitant medication				
Anticholinergics	17	17	21	19
Antidepressants	18	19	18	18
Mood stabilizers	8	11	11	9
Anxiolytics	33	37	42	37
Current alcohol abuse	2	2	4	3
Current substance abuse	2	2	2	2
Hostile behaviours	25	28	28	27
	Mean (SD)			
Age of first treatment	28.7 (10)	29.2 (11)	28.0 (10)	28.5 (10)
Years since onset	10.6 (10)	10.7 (11)	14.0 (12)	11.9 (11)
CGI overall	4.2 (1.0)	4.2 (1.0)	4.8 (0.8)	4.4 (1.0)
CGI positive	3.7 (1.4)	3.6 (1.5)	4.1 (1.4)	3.8 (1.4)
CGI negative	3.9 (1.2)	3.8 (1.3)	4.6 (1.1)	4.1 (1.3)
CGI cognitive	3.6 (1.3)	3.5 (1.3)	4.2 (1.2)	3.8 (1.3)
CGI depressive	3.4 (1.3)	3.3 (1.3)	3.6 (1.3)	3.5 (1.3)
BMI	25.9 (4.5)	26.5 (5.1)	26.6 (5.0)	26.3 (4.8)